

# Newly-published studies further underscore the value of novel, non-invasive testing in patients with NASH, Fatty Liver

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As part of the **First International NASH Day**, OWL Metabolomics proudly announces the very recent publication of 3 scientific papers that specifically evaluate the utility of metabolomics-based laboratory testing in a variety of non-alcoholic steatohepatitis (NASH) clinical applications. A metabolomics-based analysis, typically performed using a patient's serum sample, aids in the non-invasive diagnosis of the presence of NASH and, in the future, could potentially expand the use of personalized drug treatments in affected patients.

Such blood-based assays are safe, highly convenient and do not rely on the need for in-clinic technologies or technicians to perform the diagnosis. As a result, OWL Metabolomics and some other specialty laboratories have been focusing on developing novel, non-invasive alternatives to diagnostic processes such as the invasive and expensive liver biopsy, still today's gold standard for determining the presence of NASH in a patient suspected of such disease.

Three new publications below summarize the latest status of OWL technology applied to various forms of testing for patient status. These three publications address the following NASH topics:

1. Validation of OWL assays as an early-stage non-invasive tool for stratifying patients with NASH, NAFL or normal liver;
2. Application in the controlled T2DM patient population, a cohort long known for having comorbidities such as NASH at a fairly young age;
3. Adoption of metabolomic profiling in the setting of a NASH clinical trial to determine drug impacts on lipids and to verify appropriate randomization of the treatment cohorts at baseline.

## 1. Metabolomic-based non-invasive serum test to diagnose NASH: Results from Discovery and Validation Cohorts

Mayo, et al, *Hepatology Communications*, May 2018

### Study purpose: Blind validation versus Liver Biopsy

This very recent validation study further corroborates the clinical diagnostic performance of the OWL serum assays in the setting of fatty liver and NASH based on blinded comparison of the non-invasive tests to liver biopsies, widely considered the definitive diagnosis in the affected patient population.

Prior to this latest validation trial, an initial discovery trial was performed with the OWL assays in a cohort of 467 patients (246 NAFL; 131 NASH, 90 normal liver), as determined by blinded liver biopsy histology.

Overall test performance for discriminating NAFL from NASH was 0.95 AUROC (Sens., Spec., PPV and NPV of 0.83, 0.94, 0.89 and 0.90, respectively).

The blind validation study included an independent cohort of 192 patients (109 NAFL, 76 NASH, 7 NL), with diagnosis confirmed in blinded fashion using liver histology. The diagnostic performance of the validated assays produced an AUROC of 0.81 (Sens. and Spec. of 0.73, 0.80, respectively).

The test is robust in both non-diabetics and controlled diabetics within a BMI range of 25 to 45, but it is not predictive in late-stage NASH F4 or NASH cirrhosis.

The authors summarized their research by stating "the assessed non-invasive lipidomic serum tests distinguish between NAFLD and normal liver, and between NASH and NAFL with high accuracy".

**Literature citation-** <https://aasldpubs.onlinelibrary.wiley.com/doi/full/10.1002/hep4.1188>

## 2. Use of a Metabolomic Approach to Non-Invasively Diagnose Nonalcoholic Fatty Liver Disease in Patients with Type 2 Diabetes Mellitus

Bril, et al, Diabetes, Obesity and Metabolism, March 2018

**Study purpose: To assess the utility of existing metabolomics-based algorithms to classify liver disease in patients with type 2 diabetes mellitus (T2DM)**

There is a large need to develop simpler, non-invasive tests to diagnose and stratify those Type-II diabetic patients with normal liver, fatty liver and/or NASH. Despite the high prevalence of liver pathologies in T2DM, there is a paucity of published material documenting the usefulness of tests specific to the T2DM patient population. This study was an effort to determine whether existing OWL assay algorithms for NAFL and NASH were sufficient in diagnosing NASH in diabetics with controlled or uncontrolled glycemic control.

The study included 220 multi-ethnic diabetic patients whose diagnosis was NASH or NAFLD based on a combination of MRI or liver biopsy. The patients' serum samples were assayed in blinded fashion with the current OWL assays for the diagnosis of NASH or NAFL. Interestingly, the test performed best in those T2DM patients who mirrored the patient profiles recorded in the previous discovery and validation cohorts described in the first study. When compared to liver histologies, OWL assays performed sub-optimally in those diabetic patients who had either poor glycemic control or high insulin resistance. Among the Caucasian patients with good glycemic control (i.e., HbA1c <7.0%), the assay delivered an AUROC of 0.79. In that group of controlled diabetics with lower insulin resistance (i.e., HOMA-IR <3) and no cirrhosis, the blinded OWL test performance was even higher with an AUROC of 0.87 versus liver biopsy.

In short, using a revised test algorithm in the sub-population of T2DM patients with higher HbA1c levels and higher insulin resistance based on the HOMA-score is highly desirable.

**Literature citation-** <https://onlinelibrary.wiley.com/doi/full/10.1111/dom.13285>

## 3. Randomized clinical trial: a leucine-metformin-sildenafil combination (NS-0200) vs. placebo in patients with non-alcoholic fatty liver disease

Chalasani, et al, Alimentary Pharmacology and Therapeutics, June 2018

**Purpose of metabolomic testing: to track metabolomic profiling in the setting of a NASH clinical trial to determine drug impacts of NS-0200 on lipid sub-fractions linked to NAFLD and to verify appropriate randomization of the treatment cohorts at baseline**

This exploratory, randomized Ph-II, double-blind NASH drug trial was designed to assess a combination therapy's effects on liver fat in patients using PDFF-MRI (a quantitative scanning biomarker that describes degree of hepatic steatosis); secondary endpoints included standard liver assays, standard blood tests and metabolomic profiling with the OWL technology.

Circulating metabolites were collected under fasting conditions at T= 0, 8 and 16 weeks (end of trial). The detailed metabolic profiles demonstrated dose-related reductions in metabolically-active lipids, including diglycerides, triglycerides, ceramides and multiple phospholipid + sphingomyelins and glycerophospholipid species in the treatment versus placebo arms of the trial. An interesting discovery after data analysis was a separation of treatment response between the participants with baseline ALT's > 50 U/L versus those patients with ALT-values <50 U/L. Only the high ALT-group demonstrated significant treatment effects on metabolically-active lipids. The high ALT group also revealed a baseline metabolic signature characteristic of more pronounced disease, while the low ALT group did not. This outcome was consistent with other reports demonstrating weak efficacy of NASH drug candidates in mild disease vs. greater drug impact on NASH resolution with more advanced disease patients.

The placebo treatment group showed an unexpectedly high response based on PDFF-MRI assessments, but almost no response based on the lipidomic profile assessment.

Upon examination of the metabolomic signatures of the placebo and active-treatment cohorts, it was noted that the placebo arm had significantly lower levels of metabolically-active lipids (DG, TG, cholesterol esters, glycerophospholipids, ceramides and sphingomyelins) than was identified in the 2 active treatment arms, indicating the likelihood of non-comparability / lack of adequate randomization between treatment arms vs. placebo at study outset.

**Literature citation-** <https://onlinelibrary.wiley.com/doi/abs/10.1111/apt.14674>

## **About NASH, fatty liver**

Non-alcoholic steatohepatitis (NASH), a clinically-relevant and progressed form of non-alcoholic fatty liver disease (NAFLD), is histologically defined as the presence of fat (steatosis) together with inflammation and hepatic damage.

NASH is a progressive lesion that can evolve to a major hepatic damage, advanced fibrosis, cirrhosis and hepatocellular carcinoma (HCC). In the previous decades, the incidence of NAFLD has expanded rapidly and is currently the leading cause of chronic liver disease with a prevalence ranging between 10 and 40% in the adult population of Western countries, in whom approximately 10-30% progress to NASH.

In the USA, NASH is currently the second leading cause of liver transplant, and it has been estimated that it will be the first cause in the foreseeable future.

Currently, there is no approved drug for NASH and treatments are aimed to control the associated comorbidities such as obesity, diabetes and hyperlipidemia.

Today, the definitive diagnosis of NASH depends on performing an invasive liver biopsy, a medical procedure with some controversies due to the variability in sampling variation, inter-observer variability, high cost and patient safety risks. This is one reason many current NASH patients are not appropriately diagnosed.

## **About OWL Metabolomics**

OWL Metabolomics is a biotechnology company committed to the identification, validation and global commercialization of novel diagnostic assays for the liver and other prevalent human diseases, including the identification of potential therapeutic targets involved in the development of such diseases. Since its inception in 2002, OWL has pioneered unique diagnostic research within the fatty liver space, a field of considerable focus in new drug development. 'OWLiver' and 'OWLiver Care' are the world's first metabolomics-based in-vitro tests for diagnosing NASH) and NAFLD), respectively, using micro-blood samples (<0.32 ml) versus invasive liver biopsy, today's diagnostic gold-standard. OWL Metabolomics is a privately-held company based in Derio, Spain. Its main partner is the venture capital management firm Cross Road Biotech Inversiones Biotecnológicas. OWL Metabolomics collaborates globally with hospitals, liver research centers, biotechnology groups and the pharmaceutical industry. <http://www.owlmetabolomics.com/liver-disease-diagnosis.aspx>